claimed invention lacks a credible utility. See §706.03(a)(1) and 2107 of the M.P.E.P. (and particularly the discussion of the relationship between § 101 utility rejections and § 112, first paragraph rejections). Yet there is no § 101 rejection here, and the Examiner has acknowledged that the claimed methods have a credible utility. On this basis alone the rejection cannot stand.

Second, the "how to use" requirement of § 112, first paragraph is satisfied if "the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated." See § 2164.01(c) of the M.P.E.P. Applicants' specification meets this requirement (discussed in detail below).

Third, a rejection under § 112, first paragraph is only proper only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The voluminous art of record, and the declarations of Drs. Hammang, Baetge, Wahlberg and Uchida submitted herewith, demonstrate that the ordinarily skilled artisan can and has routinely practiced the claimed methods and has in fact achieved a therapeutic benefit across a wide range of disease disorders. Drs. Baetge and Hammang are named inventors and have intimate familiarity with the claimed methods; Drs. Wahlberg and Uchida have experience in neural stem cell culture and their transplantation and reflect the view of the ordinarily skilled artisan in that field.

The Rejection under § 112, First Paragraph Does Not Conform To §706.03(a)(1) M.P.E.P.

The rejection under § 112, first paragraph is based on the Examiner's assertion that transplantation according to the claimed methods does not provide a therapeutic benefit to the host. Under the case law and its interpretation in the M.P.E.P, a rejection that questions the efficacy of a claimed invention is properly analyzed as a utility rejection that must conform to the Utility Guidelines set forth in §706.03(a)(1) of the M.P.E.P. There is no § 101 rejection here, and the Examiner has conceded that the claims have a credible utility. Section 706.03(a)(1) of the M.P.E.P. makes clear that if the Examiner determines that the claimed invention has a credible utility, the rejection may not be applied. M.P.E.P. §706.03(a)(1).

In considering what constitutes a "credible utility," the Guidelines provide that, to uphold

a utility-based § 112, first paragraph rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did" (M.P.E.P. § 2107, emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (M.P.E.P. § 2107.01).

That is simply not the case here -- as is plain from the Declarations submitted herewith (discussed below), there are multiple scientific publications that confirm that transplantation of neural stem cell progeny according to the claimed methods can be routinely achieved and that a therapeutic benefit is in fact provided to the host. The Examiner has provided no evidence to the contrary.

In conformance with the Guidelines, applicants asserted multiple utilities for neural stem cell cultures and their use in the transplantation methods claimed here (see applicants' July 21, 1999 Response, p. 4 which discusses both the non-therapeutic utilities as well as the therapeutic utilities recited in the specification for the claimed methods). One of these utilities is the use of the claimed methods to provide a therapeutic benefit to the host -- and the Examiner has acknowldeged this utility as credible.

The Utility Guidelines state that "data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process" (M.P.E.P. § 2107.02(a)).[1/] Applicants have provided voluminous evidence of record here establishing utility in a wide variety of animal neurotransplantation models (detailed below).

For this reason alone the rejection should be withdrawn.

1/ Consistent with this standard, in no case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. M.P.E.P. § 2107.02(d).

The Specification Teaches One Skilled in the Art "How To Use" the Claimed Invention

The first paragraph of § 112 requires that, to enable a claimed invention, an application must describe "how to use" the invention.

In response to this rejection, applicants point out that methods for carrying out the claimed invention are described throughout the specification. See, e.g., specification, pg. 36, line 10, to pg. 42, line 13; pg. 68, line 16, to pg. 69, line 18; pg. 78, line 17, to pg. 71, line 6; pg. 96, line 12, to pg. 97, line 28 for detailed disclosure on transplanting CNS neural stem cell cultures. In addition the specification provides working examples of neural stem cell transplantation in various disease models, including, *e.g.*, Huntington's disease, Parkinson's disease, and cardiac arrest. *See, e.g.*, specification, pp. 96-101. In addition, the specification teaches and discloses the types of diseases to which the invention is directed. *See* pg. 40, lines 9-18. The specification also provides exemplary teaching of where to transplant the cells of the claimed invention. (*See, e.g.*, pg. 38, lines 17-30). Further, the specification teaches and discloses how to monitor the transplanted cells. (*See* pg. 39, lines 16-31).

In addition, each of the declarants here has unequivocally stated that the ordinarily skilled artisan would know how to use the invention as claimed. See Hammang Decl. ¶ 8; Wahlberg Decl. ¶ 8; Baetge Decl. ¶ 8; Uchida Decl. ¶ 8.

Applicants also note that skilled medical practitioners have routinely carried out cell and tissue neural transplantation as of the filing date of this application. Applicants refer the Examiner to Neural Grafting in the Mammalian CNS, Bjorklund and Stenevi, eds., (1985) Das, Ch. 3 pp. 23-30; Freed, Ch. 4, pp. 31-40; Stenevi et al., Ch. 5, pp. 41-50; Brundin et al., Ch. 6, pp. 51-60; David et al., Ch. 7, pp. 61-70; Seiger, Ch. 8, pp. 71-77 (1985). This reference provides detailed guidance relating to neural transplantation of cells into the central nervous system, e.g., parenchymally, into the ventricular cavities or subdurally onto the surface of a host brain.

Indeed, such cell and tissue neurotransplantation protocols have become increasingly common. In short, methods of neural transplantation using cells or tissue can be and are administered in accordance with standard practices of medicine as of the filing date of this application. Dr. Wahlberg makes this plain in his declaration:

> "In addition, based on my personal experience, I believe that the ordinarily skilled artisan would know how to actually carry out the step of transplanting the neural stem cell cultures of this invention according to the claimed methods given that the art is

> replete with examples of transplantation of various other tissues or cells into various parts of the brain (witness, e.g., transplantation of porcine neural cells and fetal human cells). For this reason, in my view, it cannot be disputed that the ordinarily skilled artisan, with the specification in hand, would be able to transplant neural stem cell cultures into a host; that is, the ordinarily skilled artisan would know how to use the invention as claimed." Wahlberg Decl. ¶ 8

No additional enablement is needed, and, as stated by the Federal Circuit in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1984): "A patent need not teach, and preferably omits, what is well known in the art."

Thus, because applicants have provided an enabling description of "how to use" the claimed invention, the "how to use" requirement of § 112 has been satisfied and this rejection should be withdrawn.

One of Ordinary Skill in the Art Can and Has Used the Claimed Invention Without Undue Experimentation.

Under 35 U.S.C. § 112, first paragraph, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Even if the experimentation required is complex, it is not necessarily undue if artisans skilled in the relevant art typically engage in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm. 1983).

The factors used to determine whether experimentation is undue include, but are not limited to the following: (1) the breadth of the claims; (2) the nature of the invention; (3) the amount of direction provided by the inventor; (4) the existence of working examples; (5) the level of predictability in the art; (6) the state of the prior art; (7) the level of one of ordinary skill in the art; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 858 F.2d at 737. No one of these factors is dispositive and the Examiner must consider the evidence as a whole. *Id.*; M.P.E.P. § 2104.01(a). Here, each of the declarants have stated that it is their view that the claimed methods are enabled and that the ordinarily skilled artisan would be able to routinely carry out the claimed transplant methods. See Hammang Decl. ¶ 4, 26; Wahlberg Decl. ¶ 4, 25; Baetge Decl. ¶ 4, 25; Uchida Decl. ¶ 4.

Moreover, in order to make an enablement rejection, the Examiner has the burden to establish a reasonable basis to question the enablement for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); M.P.E.P § 2164.04. In view of the evidence and arguments submitted herewith, the Examiner cannot meet this burden -- and the Examiner has not provided any evidence or factual support that would establish such basis for the rejection.

Applicants note that the specification provides an extraordinary amount of direction concerning how to practice the claimed invention. The declarants unequivocally concur that the specification provides ample guidance to the ordinarily skilled artisan -- see Hammang Decl. ¶ 8; Wahlberg Decl. ¶ 8; Baetge Decl. ¶ 8; Uchida Decl. ¶ 8. By way of example, the instant specification teaches and discloses the types of diseases to which the invention is directed. (*See* page 40, lines 9-18). Applicants have also disclosed treatment of neurodegenerative disease using progeny of human neural stem cells proliferated *in vitro* and the specification provides several working examples of transplantation of stem cell cultures including remyelination in myelin deficient rats; remyelination in human neuromyelitis optica; and remyelination human Pelizaeus-Merzbacher disease. (*See* Specification, Examples 14-17; pages 96-101). The specification also teaches and discloses where to transplant the cells of the claimed invention. (*See, e.g.*, page 38, lines 17-30). Further, the specification teaches and discloses how to monitor the transplanted cells. (*See* page 39, lines 16-31). Additionally, the specification teaches and discloses how to get the transplanted cells to proliferate *in vivo*. *See* page 52, line 14 through page 47, line 26. In addition to this direction concerning how to practice the invention, the inventors provided forty-five (45) *in vitro* and *in vivo* examples.

According to the Examiner, the pending claims are not enabled because "the specification does not provide specific guidance for producing a therapeutic effect without undue experimentation." (Office Action at page 7). None of independent claims (claims 26 and 52) recites a therapeutic benefit. Accordingly, none of the pending claims needs to show such a therapeutic benefit. Thus, while Applicants are not required to demonstrate a therapeutic benefit, Applicants have, in fact, done so.

Applicants have previously provided clear evidence of enablement, and specifically a "therapeutic benefit" in Dr. Hammang's December 2000 Declaration (as well as the evidence presented in Applicants' July 1999 Response) supporting enablement. In addition to Dr. Hammang's December 2000 Declaration, Applicants have submitted herewith unequivocal

evidence presented by Drs. Hammang, Baetge, Wahlberg and Uchida, that confirm enablement of the claimed methods. In particular, the ordinarily skilled artisan would reasonably expect that the claimed transplantation methods would provide a therapeutic benefit because (1) the transplanted neural stem cell cultures secrete cellular products which are capable of providing a therapeutic benefit to the host, and (2) the neural stem cell cultures exhibit tissue-specific differentiation upon transplantation. As the declarants have each stated, either of these facts would inescapably lead the ordinarily skilled artisan to conclude that transplantation of such neural stem cell cultures would have a reasonable expectation of success in providing a therapeutic benefit to the host. See Hammang Decl. ¶ 10; Wahlberg Decl. ¶ 10; Baetge Decl. ¶ 10; Uchida Decl. ¶ 10.

Specifically, transplantation according to the claimed methods produced a therapetic benefit in numerous different well accepted animal models, including:

1. **delivery of a secreted cellular product to produce a therapeutic benefit of neuronal sprouting and sparing in well accepted animal models of ischemia and Huntington's disease** (see Hammang Decl. ¶ 11-14; Wahlberg Decl. ¶ 11-14; Baetge Decl. ¶ 11-14; Uchida Decl. ¶ 11-14).

2. **transplantation to provide a therapeutic benefit of improved cognitive function in a well accepted animal model of age related cognitive deficit** (see Hammang Decl. ¶ 16; Wahlberg Decl. ¶ 16; Baetge Decl. ¶ 16; Uchida Decl. ¶ 16)

3. **transplantation to provide a therapeutic benefit of remyelination in a well accepted aminal model of a demyelinating disorder to provide near normal conduction velocities in the remyelinated axons** (see Hammang Decl. ¶ 17; Wahlberg Decl. ¶ 17; Baetge Decl. ¶ 17; Uchida Decl. ¶ 17). For additional discussion of other remyelination reports using the claimed methods and the therapeutic benefit conferred thereby, see Hammang Decl. ¶ 20-23; Wahlberg Decl. ¶ 20-22; Baetge Decl. ¶ 20-22.

4. **transplantation to provide a therapeutic benefit of neuronal repopulation in a well accepted animal model of retinal ischemia-reperfusion injury and mechanically injured adult retina** (see Hammang Decl. ¶ 18-19; Wahlberg Decl. ¶ 18-19; Baetge Decl. ¶ 18-19; Uchida Decl. ¶ 18-19)

5. **transplantation to provide a therapeutic benefit of replacing lost or deficient neural populations in a well accepted animal models** (see Hammang Decl. ¶ 24-26; Wahlberg Decl. ¶ 23-25; Baetge Decl. ¶ 23-25).

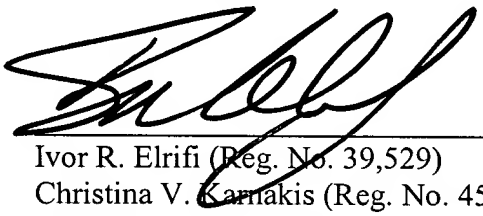
Finally, the declarants have referred the Examiner to additional publications that in their view reflect the view of the art that the claimed methods would provide a therapeutic benefit to the host. See Hammang Decl. ¶ 27; Wahlberg Decl. ¶ 26; Baetge Decl. ¶ 26; Uchida Decl. ¶ 20.

As the M.P.E.P. directs, "if any use is enabled when multiple uses are disclosed, the application is enabling for the invention". M.P.E.P § 2164.01(c). Here multiple uses of the claimed methods are disclosed, and applicants have provided unrefuted evidence that the claimed methods have been carried out in the art without undue experimentation and have, in fact, produced a therapeutic result. For all the foregoing reasons, the rejection should be withdrawn -- the pending claims are enabled.

CONCLUSION

On the basis of the foregoing, Applicants respectfully request that the rejection of the pending claims be withdrawn. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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